Dual action of glatiramer acetate (Cop-1) in the treatment of CNS autoimmune and neurodegenerative disorders

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Protective autoimmunity is the body's defense mechanism against destructive self-compounds such as those commonly associated with neurodegenerative disorders. Autoimmune disease and neurodegenerative disorders can thus be viewed as two extreme manifestations of the same process. Therefore, when designing therapy, it is important to avoid an approach that will cure the one by invoking the other. One way to stop, or at least slow down, the progression of neurodegeneration without risking development of an autoimmune disease is by boosting protective autoimmunity in a well-controlled way. Copolymer 1 (Cop-1), an approved drug for the treatment of multiple sclerosis, can be used as a treatment for autoimmune diseases and as a therapeutic vaccine for neurodegenerative diseases. We propose that the protective effect of Cop-1 vaccination is obtained through a well-controlled inflammatory reaction, and that the activity of Cop-1 in driving this reaction derives from its ability to serve as a 'universal antigen' by weakly activating a wide spectrum of self-reactive T cells.

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Neurodegenerative disorders are commonly associated with ongoing neuronal loss in the central nervous system (CNS) [1,2]. Following the loss of neurons caused by primary risk factors, additional ('secondary') neuronal loss is mediated by self-compounds, such as glutamate, nitric oxide or reactive oxygen species, that exceed their physiological concentrations. These compounds are implicated in various types of neurological disorders and acute CNS injuries [3–7]. It is interesting to note that destructive components common to neurodegenerative diseases have also been identified in autoimmune diseases such as multiple sclerosis (MS); in this disease, myelin damage in the CNS is accompanied by subsequent neuronal loss [8–11].

Immune activity in the CNS has long been considered detrimental, and patients with neurodegenerative disorders and acute injuries are therefore commonly treated with immunosuppressive drugs [12–17]. This negative view of inflammation derives largely from the fact that the presence of immune cells in the brain has been reported mainly in pathological situations. Indeed, these cells came to be regarded as the cause of the pathology, not as the result, and certainly not as cells recruited for the purpose of physiological repair. Thus, for example, the immune components (e.g. activated microglia, blood-borne macrophages, CD8 and CD4 T cells) found in damaged regions and plaques in patients with neurodegenerative syndromes were assumed to be causatively associated with the syndrome [18,19]. However, studies in the past few years have shown that immune cells, in particular autoimmune T cells, play an essential role in protecting the injured CNS from the ongoing spread of damage [20–25]. Moreover, it has proved possible to boost protective immunity in rats and mice without risk of inducing neurodegenerative disease, as will be discussed here.

Autoimmune neuroprotection – a physiological self-repair mechanism

In certain strains of rats, passive transfer of autoimmune T cells reactive to myelin-related self-antigens induces a transient autoimmune syndrome known as experimental autoimmune encephalomyelitis (EAE) [26,27]. If these strains of rats are subjected either to partial crush injury of the optic nerve or to contusive injury of the spinal cord, the autoimmune cell transfer not only induces EAE but also confers neuroprotection by reducing secondary degeneration of the damaged neural tissue [21,23]. Recent studies have provided persuasive evidence that the observed autoimmune neuroprotection is not merely the outcome of an experimental manipulation, but is a physiological response evoked systemically by the CNS injury [20,28]. Furthermore, in several strains of mice and rats, an absence of mature T cells (e.g. in nude mice or in rats subjected to thymectomy at birth) results in a worse outcome from CNS injury than in their wild-type counterparts [20,28].

The way in which autoimmune T cells prevent the degenerative consequences of CNS insults or protect the injured nerve from self-destructive mediators of toxicity is currently under intensive investigation. Studies have shown that active autoimmune T cells engage in a dialogue with CNS-resident microglia or with infiltrating macrophages [29]. Among the effects attributed to such dialogue is activation, through MHC class II interaction, of the affected cells, enabling them to clear the injury site of potentially harmful factors, such as destructive self-compounds. On the basis of the ability of activated T cells and monocytes to produce neurotrophic factors, it was further suggested [30,31] that macrophages might serve as a source of neurotrophins. Thus, T cells might participate in the activation of macrophages, through MHC class II interaction, for the production of such factors. However, it was recently shown that the autoimmune T cells are not the only T cells participating in autoimmune neuroprotection, but that another population of

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CD4 T cells (probably of a regulatory phenotype) is also an essential participant (J. Kipnis et al., unpublished).

The phenotype of the T cells that regulate neuroprotection is still unknown. The most promising candidates are naturally occurring CD4 CD25 regulatory T cells, which are antigen specific, and natural killer cells, which play an important role in terminating EAE [32]. In view of the results described above, it is reasonable to suggest that nonspecific therapeutic suppression of the immune response to CNS trauma (e.g. by depriving the body of proinflammatory cytokines) might be harmful for neurons in the long term. This might be the case even though the immune involvement appears to be at some cost in terms of neuronal loss to the tissue, since the benefit of neuroprotection afforded by the ongoing immune activity, if well controlled, will eventually outweigh the cost. It therefore seems that a preferable therapy would be antigen-specific immunomodulation aimed at boosting and regulating the inflammatory response [33,34] to a CNS insult [24].

It was recently discovered that it is possible to boost protective immunity in rats and mice without the risk of inducing EAE, by vaccinating the injured animal with glatiramer acetate (Cop-1) [35], a drug used clinically to alleviate the symptoms of MS. Vaccination with Cop-1 emulsified in a strong adjuvant reduced glutamate-mediated cytotoxicity in the rodent retinal ganglion cell (RGC) model and attenuated the symptoms of a chronic neurodegenerative disorder (simulating glaucoma) in a rat model of high intraocular pressure [35,36]. The following sections discuss the dual effects of Cop-1 in protecting against 'destructive' autoimmunity (seen in patients with autoimmune diseases such as MS) and in inducing or boosting 'protective' autoimmunity, thereby promoting neuronal survival in cases of neurodegenerative disorders.

Cop-1 in autoimmune disease

Cop-1 (Copaxone) is a synthetic amino acid polymer (4.7 11 kDa) composed of four amino acids (L-alanine, L-lysine, L-glutamic acid and L-tyrosine) in a defined molar ratio [37,38]. It was originally synthesized to mimic the activity of myelin basic protein (MBP) by inducing EAE in laboratory animals [39], but was found to be non-encephalitogenic and even to suppress MBP-induced EAE [40]. Cop-1 blocks chronic-relapsing EAE induced in a (SJL/J BALB/c) F_1 mouse model by application of mouse spinal cord homogenate or encephalitogenic peptides of proteolipid protein (PLP) [41]. The polymer is thought to bind to the relevant MHC proteins and to activate suppressor T cells triggered by determinants common to Cop-1 and MBP [39].

The precise mechanisms by which Cop-1 prevents the development of EAE and ameliorates MS are not yet fully understood. Nevertheless, some important immunological properties of this copolymer have been discovered. Cop-1 shows partial cross-reactivity with MBP, mediated both by T cells and by antibodies. Cop-1 can serve as an antagonist of the T-cell receptor for the immunodominant MBP epitope [42]. It can also bind to various MHC class II molecules [43] and prevent them from binding to T cells with several antigen-recognition properties. In a recently published commentary [44], Hafler refers to Cop-1 as a 'universal APL (altered peptide ligand)' or a 'universal antigen', and formulates a novel view of the effect of Cop-1 in patients with MS. In rodents, Cop-1 suppresses the encephalitogenic effect of autoreactive T cells. Passive transfer of Cop-1-specific T cells was found to prevent the development of EAE induced in rats or mice by MBP [45], PLP [41], or whole spinal cord homogenate [46]. In humans, daily administration of Cop-1 resulted in the development of a T helper 2 (Th2)/Th3-type response over time [47].

Low-affinity self-reacting T cells are activated by Cop-1: a 'safe' therapeutic vaccine for neurodegenerative disorders

An initial assumption was that Cop-1, by cross-reacting with MBP or other components of myelin, might enable Cop-1-specific T cells to recognize the damaged tissue, accumulate there, and undergo activation resulting in neuroprotection [35]. However, more-recent studies have shown that T cells reactive to Cop-1 do not proliferate when exposed to myelin proteins [48]. After partial crush injury of the rat optic nerve, myelin epitopes are exposed at the site of injury. Following injury, peripheral lymphocytes, regardless of their antigenic specificity, enter the CNS [49]. T cells reactive to myelin proteins are activated at the site of injury or in the cervical lymph nodes, where the drainage of CNS antigens probably takes place [50,51]. Recent studies have shown that activation of autoimmune T cells after injury is a prerequisite for neuroprotection, and that such activation can be boosted by immunization with self-antigens (in this case myelin proteins) [21,22,52]. These findings led us to suggest that, upon passive transfer of Cop-1-specific T cells or active immunization with Cop-1, T cells arriving at the site of injury will serve a dual role: first they will trigger proinflammatory activity and later they will terminate their own activation [35]. Indeed, examination of this possibility showed not only that Cop-1-reactive T cells accumulate in the normal (undamaged) optic nerve, where only myelin-specific T cells can accumulate, but also that their numbers are smaller than those of the accumulated myelin-specific T cells [35]. These findings pointed to cross-reactivity of Cop-1-activated T cells with myelin proteins in vivo. Activated Cop-1-reactive T cells produce neurotrophic factors, but their pattern of neurotrophin expression might differ from that of MBP-reactive activated T cells [35]. Accordingly, it was suggested that Cop-1-reactive T cells, after arriving at the site of the injury, are weakly reactivated by self-antigens residing at the lesion site. Such reactivated T cells were shown to produce cytokines associated with both Th1 (interferon) and Th2 (interleukin 4) [35], indicating that Cop-1-reactive T cells are potentially capable of self-regulation. We suggest that the reactivated proinflammatory Cop-1-reactive T cells in turn activate the resident microglia (as suggested above),

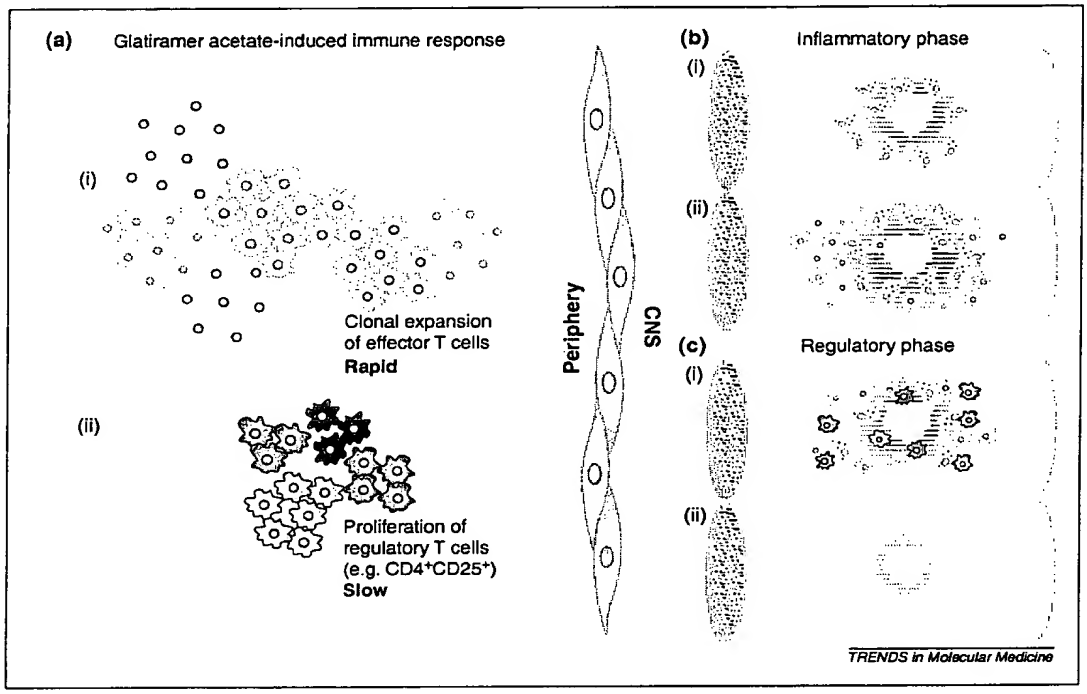

Fig. 1. Model of a two-step (effector and regulatory) immune response to immunization with Cop-1. (a) Immunization with the weak 'universal antigen' Cop-1 activates T-cell clones with different antigenic specificities. (i) Effector cells, possibly of a T helper 1 (Th1) phenotype, which are known to respond rapidly to the antigen, are the first to proliferate in the periphery; (ii) the slower proliferating population of regulatory T cells (possibly of Th2/Th3 phenotype, and/or naturally occurring regulatory CD4 CD25 T cells) respond later. After being activated at the periphery, these T cells migrate to the injury site in the central nervous system (CNS). (b) (i) At the site of injury, the CNS-resident microglia, activated by the injury itself, start to present CNS antigens and to activate and attract peripheral immune components; (ii) the first to arrive are the Cop-1-activated effector T cells, which upregulate the activation state of microglia, enhancing their phagocytic and antigen-presenting capacities. (c) (i) At a later stage, regulatory (suppressor) T cells accumulate at the site of CNS injury until the ratio of regulatory T cells to effector T cells is high enough to inhibit effector action and to terminate the inflammatory response; (ii) in this way, they protect undamaged neurons from the toxic effects of the environment, thus increasing neuronal survival.

enabling them to clear the lesion site of toxic self-compounds and to display enhanced phagocytic activity for nonspecific clearance. In addition, these T cells might activate microglia to produce neurotrophic factors.

According to the above scenario, passive transfer of activated Cop-1-reactive T cells leads to their accumulation at the site of injury, where they reinforce the local immune response (inflammation) at the injury site. However, this interpretation of activity as an outcome of cross-reactivity with MBP has turned out to be an oversimplification: Cop-1-activated T cells were also found to be neuroprotective in other models of CNS injury, where myelin-associated antigens are not active, such as the insult caused by direct exposure of RGCs to glutamate toxicity or the death of RGCs resulting from increased intraocular pressure in a model of high-tension glaucoma [36]. The question then arises: how can Cop-1 vaccine be effective under conditions where myelin-related vaccines are not? These results point to the possibility of cross-reactivity between Cop-1-reactive T cells and other self-proteins.

Cop-1 cross-recognizes T cells reactive to various antigens, and it might bind MHC class II molecules without being processed [53]. It is possible that Cop-1 acts as a universal antigen, as suggested by Hafler [44]. Furthermore, vaccination with Cop-1 activates different T-cell clones with a wide range of antigenic specificities [54,55] and some of these clones might weakly cross-react with epitopes of myelin antigens, boosting the endogenous response to white matter injury; by contrast, others might weakly cross-react with retinal-exclusive peptides (or with self-antigens in other tissues), inducing a protective immune response in the retina when protection of RGCs from glutamate toxicity is required. We suggest that T cells reactive to Cop-1 should be referred to not as Cop-1-specific T cells, but as low-affinity self-reactive T cells activated by Cop-1. According to this view, Cop-1, being a weak self-reactive antigen, will weakly activate numerous self-reactive T cells. These T cells will therefore slowly undergo proliferation, which will be balanced to some extent by the proliferation of regulatory T cells also activated by Cop-1. Since the rate of proliferation of the regulatory clones (e.g. naturally occurring CD4 CD25 regulatory T cells) is slower than that of the effector (self-reactive) T cells [56], there is a period of time in which effector Th1 cells can act without being suppressed by regulatory T cells (Fig. 1). This scenario is in line with our recent suggestion that a pro-inflammatory immune activity is a prerequisite for neuroprotection, but that it must be stopped on time (J. Kipnis et al., unpublished).

Cop-1 as an immunomodulator in cases of inflammation

As discussed above, Cop-1 provides effective treatment both for MS [57] and for injuries of the CNS [35,36]. The question then arises: do the two types of disorders have common features that could explain why the same compound, when administered according to a suitable therapeutic regimen, is effective in both? Or do the unique features of Cop-1 as a weak universal self-antigen make it suitable for different indications? The principal common characteristic of the two conditions is inflammation. This appears to be a feature not only of autoimmune neurodegenerative

diseases (such as MS) but also of non-autoimmune neurodegenerative disorders, such as glaucoma, acute CNS injuries, Alzheimer's disease (which was recently shown to be characterized by inflammation in plaques) and different types of chronic inflammation, probably including graft rejection and graft-versus-host disease.

The fact that so many pathological conditions are characterized by inflammation is largely responsible for the poor reputation that this feature has acquired [58]. However, the available data now suggest a need for a paradigm shift away from this in the perception of autoimmune diseases and inflammation [59]. Indeed, we suggest that the autoimmune response be viewed as the individual's protective or reparative physiological response to any CNS insult, whether it be caused by exogenous invading microorganisms, by mechanical trauma, or by destructive self-compounds evoked by stress originating within the body itself. Autoimmune disease is then one extreme situation, where the autoimmune response overshoots and goes out of control. The other extreme is a degenerative disorder, where the autoimmune response is not strong enough for effective protection, and degeneration therefore continues. Thus, in both of these pathological conditions, inflammation might be present but will need to be differently handled in each case. How can treatment with the same compound (Cop-1) provide both properly regulated immune suppression (in the case of the autoimmune disease) and properly regulated immune activation (in the case of the neurodegenerative disease)?

Differential modes of Cop-1 administration in patients with MS or with CNS injury

If Cop-1 acts as a universal antigen, questions arise in connection with the optimal therapeutic regimens of Cop-1 for different conditions. Should patients with autoimmune diseases be treated in the same way as patients with acute or chronic neurodegenerative disorders? In the case of autoimmune disease, where the regulation of autoimmunity is malfunctioning, there is a need to shut off the autoimmune clones. By contrast, in the case of acute CNS injury or chronic neurodegenerative disorders (e.g. MS), there is a need for neuroprotection, initially requiring the participation of active autoimmune clones and subsequently needing tight control to shut off the autoimmune response at the appropriate time.

Reports indicate that MS patients treated with Cop-1 initially show a Th1-type response, which later switches towards Th2 [47,60], considered to be a favorable phenotype in such patients. From this stage onwards, each application of Cop-1 boosts the Th2-type response and weakens the Th1-type response, until there is no response to Cop-1 [53,61]. This eventual lack of response might reflect anergy of effector T cells (primarily specific to myelin or to other self-proteins) caused by overstimulation with Cop-1. Alternatively, or in addition, it might reflect over-activation of regulatory T-cell clones and their consequent inhibition of effector clones (regardless of their antigenic specificity). Whatever the underlying mechanism, this type of progression of the autoimmune response was found to be beneficial in patients with autoimmune diseases.

In acute neurodegenerative disorders, the aim of therapy is to boost the local immune response at the lesion site in a well-regulated way. Accordingly, the early and transient Th1 (effector) response is a welcome phenomenon, essential for stopping the process of damage caused by self-destructive compounds. It can be achieved by Cop-1 vaccination, which allows an induced Th1 (effector) immune response to be accompanied by a regulatory response. In patients with chronic neurodegenerative disorders, the timing and amount of each booster application should incorporate the Th1 phase. During this phase (which is thought to be very short), the affinity of the Th1 cells for self-epitopes is relatively low, so the development of an autoimmune disease during the Th1 phase window is avoided, whereas the desired activation of phagocytes for clearing of cell debris is probably achieved.

It is important to bear in mind that MS is now recognized not only as a disorder related to myelin, but also as a neuronal disorder [62–64]. Glutamate, a principal mediator of toxicity in neurodegenerative disorders, has also been identified in patients with MS [62,63]. Protection against the harmful effect of glutamate can be obtained by vaccination with Cop-1 [36]. Giving Cop-1 to patients with MS using the same regimen as for patients with neurodegenerative disorders might therefore be worth considering.

Concluding remarks

We suggest that the optimal application of Cop-1 for the treatment of neurodegenerative diseases is by vaccination in order to activate the weakly self-reactive Th1 cells in a well-regulated way. According to our perception of autoimmunity, the regimen for Cop-1 administration in individuals with autoimmune disease (daily injection) differs from that required for treatment after CNS injury. Future studies should be aimed at establishing the optimal regimen for Cop-1 administration in individuals with diseases that are both autoimmune and neurodegenerative, to achieve both neuroprotection (against degeneration) and arrest of the demyelination process (i.e. prevention of disease). Elucidation of the precise mechanism underlying the interaction of Cop-1-reactive T cells with self-antigens might shed light on the Cop-1-mediated protective mechanisms, which are so similar and yet so different, in autoimmune diseases and in neurodegenerative disorders.

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